PATENT COOPERATION TREATY

REC'D 08 AUG 2005
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From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	see form PCT/ISA/210 (second sheet)
Applicant's or agent's file reference	**FOR FURTHER ACTION** See paragraph 2 below
see form PCT/ISA/220	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/013549	29.11.2004	19.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07K14/47, C07K14/00, A61K6/033, A61K7/16

Applicant
HUYBRECHTS, Lucas

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION.**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/013549

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 2,6,7,9-16,25 (completely) and 1,3,4,26,27 (partially); 3-5,8,26,27 as to IA

because:

☒ the said international application, or the said claims Nos. 3-5,8,26,27 (as to IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 2,6,7,9-16,25 (completely) and 1,3,4,26,27 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 5,8,17-24 (completely) and 1,3,4,26,27 (partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8
	No:	Claims	1,3-5,17-24,26,27
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,3-5,8,17-24,26,27
Industrial applicability (IA)	Yes:	Claims	1,17-24
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III.

Claims 3-5,8,26 and 27 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Due to an objection against unity of invention (see below), a search has been performed for subject-matter of claims 5,8,17-24 (completely) and 1,3,4,26,27 (partially) only. Therefore, no opinion on novelty, inventive step and industrial applicability will be formulated for subject-matter of claims 2,6,7,9-16,25 (completely) and 1,3,4,26,27 (partially).

Re Item IV.

The separate inventions/groups of inventions are:

I: claims: 5,8,17-24 (completely) and 1,3,4,26,27 (partially)
bisphosphonylated-epsilon-polylysine, methods and uses thereof; use of proteins that are bisphosphonylated and use of epsilon-polylysine or polylysine

II: claims: 12,13 (completely) and 1,3,4,26,27 (partially)
casein phosphopeptide epsilon-polylysine copolymer, methods and uses thereof

III: claims: 16 (completely) and 1,3,4,26,27 (partially)
hydrolyzed phosvitin that has been conjugated to epsilon-polylysine, methods and uses thereof

IV: claims: 10,11 (completely) and 1,3,4,26,27 (partially)
casein phosphopeptide that has been polymerized with a carbodiimide, methods thereof

V: claims: 6,7 (completely) and 1,3,4,26,27 (partially)
phosvitin that has been hydrolyzed with trypsin, pepsin or a combination of both, methods and uses thereof

VI: claims: 2,9,14,15 (completely) and 3,4,26,27 (partially)
chitosan hydrolysate that has been conjugated with casein phosphopeptide, methods and uses thereof; use of copolymers containing hydrolyzed chitosan

VII: claim 25 (completely) and 3,4,26,27 (partially)
use of biscarboxylated epsilon-polylysine, 3-hydroxy-phthalated epsilon-polylysine or proteins that are biscarboxylated; method to produce 3-hydroxy-phthalated epsilon-polylysine

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:
The problem underlying the present application is the provision of compounds for the treatment and prevention of caries.
As a solution, peptides are used that contain phosphate- or phosphonate groups.
The technical feature which a priori could unify different solutions is the entity of being a peptide containing phosphate- or phosphonate groups.
However, such a solution has already been proposed in the prior art, see e.g. the international patent application WO 02/094204 disclosing complexes of casein phosphopeptides and amorphous calcium phosphate exerting anticariogenic properties (see pages 1 and 2), or the Japanese patent application JP5310544 describing the use of epsilon-polylysine and its phosphate salts which are useful in treatment of dental caries.
The problem to be solved may therefore considered to be the provision of further peptides contain phosphate- or phosphonate groups.
However, a structural relationship between the phosphatylated or phosphonylated peptides of the different subjects which could fulfil the role of a "special technical feature" in the sense of Rule 13 PCT is missing.
As there are no other special technical features, unity of invention is lacking, giving rise to the subjects as above.

Re Item V.

Reference is made to the following documents:

D1: WO 02/103004 A (LEVY, ROBERT, J; ALFERIEV, IVAN; FISHBEIN, ILIA) 27 December 2002 (2002-12-27)

D2: PATENT ABSTRACTS OF JAPAN vol. 018, no. 118 (C-1172), 25 February 1994 (1994-02-25) & JP 05 310544 A (CHISSO CORP), 22 November 1993 (1993-11-22)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 and 3 is not new in the sense of Article 33(2) PCT.

The document D1 discloses (the references in parentheses applying to this document): polylysine modified with bisphosphonate as chelating group for metals (see page 8).
Therefore, subject-matter of claim 1 does not meet the requirements of Article 33(2) PCT.

The document D2 discloses the use of epsilon-polylysine having anticariogenic properties (see abstract).
Therefore, subject-matter of claim 3 does not meet the requirements of Article 33(2) PCT.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 8 does not involve an inventive step in the sense of Article 33(3) PCT.
The document D2 is regarded as being the closest prior art to the subject-matter of claim 8 and discloses phosphate salts of epsilon-polylysine for treatment and prevention of caries.
The subject-matter of claim 8 therefore differs from D2 in that the epsilon-polylysine is bisphosphonylated.
The problem to be solved by the present invention may therefore be regarded as a further modified form of epsilon-polylysine for treatment or prevention of caries.
The solution proposed in claim 8 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT), since phosphonylation is merely one of

several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to be able to form a complex with calcium, in particular with view to the document D1 that discloses polylysine modified with bisphosphonyl groups as chelating group for metals.

The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claims 17,18,24,26 which therefore are also considered not new and/or inventive.

Dependent claims 4,5,19-23 and 27 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, see documents D1 and D2 and the corresponding passages cited in the search report.

For the assessment of the present claims 3-5,8,26 and 27 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.